

VISIT...

LANZAROTE
Caliente.COM

The Neurobiology of Addictive Disorders

Stephen Ross, MD,*†‡ and Eric Peselow, MD‡

Abstract: Addiction is increasingly understood as a neurobiological illness where repetitive substance abuse corrupts the normal circuitry of rewarding and adaptive behaviors causing drug-induced neuroplastic changes. The addictive process can be examined by looking at the biological basis of substance initiation to the progression of substance abuse to dependence to the enduring risk of relapse. Critical neurotransmitters and neurocircuits underlie the pathological changes at each of these stages. Enhanced dopamine transmission in the nucleus accumbens is part of the common pathway for the positively rewarding aspects of drugs of abuse and for initiation of the addictive process. γ -Aminobutyric acid, opioid peptides, serotonin, acetylcholine, the endocannabinoids, and glutamate systems also play a role in the initial addictive process. Dopamine also plays a key role in conditioned responses to drugs of abuse, and addiction is now recognized as a disease of pathological learning and memory. In the path from substance abuse to addiction, the neurochemistry shifts from a dopamine-based behavioral system to a predominantly glutamate-based one marked by dysregulated glutamate transmission from the prefrontal cortex to the nucleus accumbens in relation to drug versus biologically oriented stimuli. This is a core part of the executive dysfunction now understood as one of the hallmark features of addiction that also includes impaired decision making and impulse dysregulation. Understanding the neurobiology of the addictive process allows for a theoretical psychopharmacological approach to treating addictive disorders, one that takes into account biological interventions aimed at particular stages of the illness.

Key Words: addiction, neurobiology, pharmacotherapy

(*Clin Neuropharm* 2009;32: 269–276)

Drug addiction is increasingly recognized as a neurobiological illness whereby repetitive drug use corrupts and reorganizes the normal circuitry of rewarding and adaptive behaviors, causing drug-induced neuroplastic changes that manifest phenomenologically as recurrent, compulsive drug-seeking behaviors; an inability to regulate such behaviors; continued use of substances despite catastrophic negative consequences; continued vulnerability to relapse even after an extended period of sobriety; and a reduced drive to acquire biologically relevant natural rewards important for survival and optimal psychosocial

functioning in society.¹ By corrupting motivational and learning neurocircuitry, drugs of abuse fundamentally and sometimes permanently alter how an individual who has an addictive disorder interacts with salient environmental stimuli that come to predict reward, whether it be biologically oriented or drug-conditioned stimuli.² As such, addiction is now understood as a chronic brain illness marked by a long-term remitting and relapsing course and caused by a complicated set of interactions among several variables in the context of repeated drug intake: host (ie, biological factors such as genetic vulnerability, psychological factors such as high novelty seeking/low harm avoidance and the presence of psychiatric illness, medical illness) * drug (ie, potency, route of administration, ability to generate conditioned stimuli that come to predict reward) * environmental (ie, legality, acceptability, availability, peer pressure, economic, political) factors.

This article will review the basic neurobiology of the addictive process from drug initiation to the transition from abuse to dependence to the risk for relapse. Critical brain structures and receptors will be highlighted. In turn, this will serve as a basis to present a theoretical overview of pharmacotherapeutic interventions to treat addiction, looking at overall goals of treatment and specific targeted neurotransmitter systems.

NEUROBIOLOGY OF REWARD AND ADDICTION

To understand the neurobiological basis of addiction, we have to examine the underlying neurocircuitry and neuropharmacology involved in biologically rewarding adaptive behaviors and then examine the various stages of the addictive process: initiation of substance abuse, progression from abuse to dependence, and enduring risk for relapse.

Neurobiology of Reward

A key to understanding the addictive process is to examine the neurobiology of “natural” rewarding and adaptive behavior. On a fundamental level, organisms have adaptive, evolutionarily determined systems in place that mediate our acquisition of pleasurable rewarding behavior involved in the survival of our species (such as sex, food, social affiliation) and avoidance of aversive events whether they be psychological or physical in nature. Three main brain regions have been broadly and simplistically identified that mediate such adaptive behavior and the regulation of behavioral output: the nucleus accumbens (NA) mediating reward-related activities (positive valence); the amygdala involved in fear-motivated behaviors (negative valence); and the prefrontal cortex (PFC) involved in decision making and the prediction of rewarding behaviors by determining salience attribution of environmental stimuli and directing the intensity of the behavioral response.³ Homeostatic functioning of the interoceptive system such as internal motivational and affective states combine with external incentive stimuli that predict reward to determine the overall output of a given behavioral response by an individual in acquiring natural rewards or in avoiding and diminishing painful states of consciousness.^{4,5}

From the *Division of Alcoholism and Drug Abuse, Bellevue Hospital; †NYU Langone Center of Excellence on Addiction; and ‡Department of Psychiatry, New York University, New York, NY.

Address correspondence and reprint requests to Stephen Ross, MD, Division of Alcoholism and Drug Abuse, Bellevue Hospital, NYU Langone Center of Excellence on Addiction, New York University School of Medicine, 462 First Ave, NBV 20E7, New York, NY 10016; E-mail: Stephen.ross@nyumc.org

Sources of support: None.

Financial Disclosures: Eric Peselow, Speakers' Bureau: Forrest.

Copyright © 2009 by Lippincott Williams & Wilkins

DOI: 10.1097/WNF.0b013e3181a9163c

Neurobiology of Initiation of Addiction

Dopamine, the NA, and Reward: Initiation of Addiction (Positive Reinforcement)

A commonality among all drugs with addictive liability, in addition to naturally rewarding behaviors (ie, food, sex), is their ability to increase extracellular dopamine (DA) levels in the NA (part of the common reward mesolimbic pathway from the ventral tegmental area [VTA] to the NA) either directly by enhancing DA transmission through reuptake inhibition or facilitating presynaptic DA release (ie, cocaine, amphetamine, methylenedioxymethamphetamine) or by indirect mechanisms that affect DA cell firing (ie, alcohol, opioids, nicotine, cannabis, *N*-methyl-D-aspartic acid [NMDA] antagonists).⁶ Although DA seems to be the primary mechanism of the initiation of drug reinforcement, other neurotransmitters have been implicated indirectly in the acute reinforcing properties of substances of abuse: γ -aminobutyric acid (GABA), opioid peptides, serotonin, acetylcholine, endocannabinoids, and glutamate. These systems may work in conjunction with the mesolimbic DA system or may constitute independent pathways of reinforcement.⁷

GABAergic interneurons provide afferent inhibitory modulation on the release of DA in the VTA and NA, and recent pharmacologic agents that enhance GABAergic function have been tried with some success in treating cocaine, alcohol, and nicotine use disorders.^{8,9}

The opioid system plays a modulatory role on the dopaminergic system where activation of mu opioid receptors increases DA transmission, most likely by inhibiting GABAergic interneurons that normally provide tonic inhibition to dopaminergic neurons in the VTA.¹⁰ In addition to mediating the reinforcing properties of opioids, the opioidergic system has also been implicated in the reinforcing properties of alcohol and possibly cannabis and may play a role in impulse control disorders such as pathological gambling.¹¹

Regarding the serotonergic system, given the VTA and NA receive serotonergic afferents from the raphe nucleus and that studies of platelet monoamine oxidase B (a peripheral marker of 5HT function) have shown low levels in subjects with substance use disorders and pathological gambling,¹¹ it is possible that 5HT's dysfunction in impulse control disorders reflects inhibitory impairment of the PFC, and it is possible that serotonergic compounds can modulate the mesolimbic DA pathway.¹²

Cholinergic neurons from the pedunculopontine or laterodorsal tegmental nucleus provide excitatory input to the VTA, causing release of DA in the projection from the VTA to the NA. Nicotinic cholinergic $\alpha_4\beta_2$ receptors have been strongly implicated in the reinforcing properties of nicotine, whereas M_5 muscarinic receptors have been implicated in the rewarding effects of opioids and cocaine.⁹

With respect to the endocannabinoid system, the cannabinoid type I (CB1 receptor) mediates the reinforcing properties of cannabinoids that facilitate the release of DA in the NA through an unclear mechanism. In addition, given that rimonabant (a CB1 inverse agonist and antagonist) has been associated with blocking the reinforcing properties of cannabis, opioids, alcohol, cocaine, and nicotine in animal paradigms, activation of the endocannabinoid system may play a role in the motivational, DA releasing, and reinforcing properties of several drugs of abuse. As part of this, CB1 antagonists/inverse agonists represent a potential class of antiaddictive pharmacotherapies.

In terms of glutamate, excitatory glutamatergic input from a variety of cortical structures (including the PFC) stimulates DA release in the VTA and NA.¹³ Paradoxically, this may be how certain NMDA antagonists (ie, phencyclidine, ketamine, dex-

tromethorphan) exert their reinforcing properties. A theoretical explanation is that NMDA antagonists (ie, ketamine) may actually enhance glutamatergic transmission by disinhibiting glutamate release, shunting glutamate to the other glutamatergic receptors other than NMDA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, kainite, and the metabotropic G protein-coupled glutamate receptor) and causing a hyperglutamatergic state.¹³ There is some evidence to suggest that NMDA receptor blockers may antagonize GABA neurons with a greater potency than their inhibition at the NMDA receptor.¹⁴ The NMDA antagonism may therefore diminish activation of GABA inhibitory neurons, with a diminution of cortical extracellular GABA levels that in turn would decrease GABA's normal inhibition of glutamate neurons, causing a net disinhibition of glutamate neurons and an increase in glutamatergic transmission in non-NMDA glutamate receptors.¹⁵ In turn, cortical glutamatergic activation stimulates monoaminergic terminals within the cortex, limbic system, midbrain, and brain stem.¹³ As part of this, extracellular DA levels are increased in reward-related areas (ie, VTA and NA), thereby likely explaining certain NMDA antagonists' (ie, PCP, ketamine) addictive potential. However, in addition to NMDA antagonists having addictive liability, they have also been associated with antiaddictive effects in humans, including memantine (NMDA antagonist) in alcohol^{16,17} and opiate use disorders,¹⁸ acamprosate (weak direct NMDA antagonism and direct interaction with the metabotropic glutamate receptor type 5, thereby indirectly acting as an inhibitory modulator at the NMDA receptor) for alcoholism,¹⁹ ibogaine (NMDA antagonism as one of its many receptor actions, although its exact antiaddictive mechanism remains unknown as 18-methoxyoronaridine, a congener of ibogaine has antiaddictive properties without appreciably antagonizing the NMDA receptor) for opiate withdrawal,²⁰ and ketamine (NMDA antagonist) in patients with alcohol and opiate use disorders.^{21,22} Speculatively, a simplistic heuristic divide might be that antagonist effects at the NMDA receptor confer the relative antiaddictive properties of a specific NMDA antagonist, and its hyperglutamatergic effects may confer its addictive liability. Therefore, the relative balance or ratio of NMDA blockade to enhanced glutamate transmission (which may be a function of dose, route of administration, relative potency at the NMDA receptor, and pharmacokinetic/pharmacodynamic interindividual variation) may explain why some NMDA antagonists are more reinforcing than others and why some may have greater antiaddictive properties.²³

The initial event of enhanced dopaminergic transmission in the NA from the various drugs of abuse is responsible for the acute "high" or initial reinforcing effects (ie, positive reinforcement) of drugs of abuse. In animals, lesioning the NA or impeding DA release into the NA diminishes the acquisition of drug-seeking behaviors and markedly attenuates drug self-administration.²⁴ Drugs of abuse are able to more rapidly and markedly elevate NA DA levels to supraphysiological levels for sustained periods of time compared with natural rewards and as such are more compelling reinforcers that effectively outcompete natural reinforcers and end up "hijacking" and corrupting the initial process of reward processing. One of the earliest theories of addiction postulated that the recurrent drive for pleasure or positive reinforcement was at the heart of the addictive process.²⁵ However, we know that as a core feature of addiction, the behaviors persist despite tolerance to the positive effects of drugs over time, and that individuals maintain their use of substances through negative reinforcement to avoid negative states of consciousness such as withdrawal states or to self-medicate for underlying psychic distress. In addition, the hedonic nature of a substance does not necessarily predict its

addictive liability. For example, nicotine has greater addictive liability in humans than even intravenous heroin or crack cocaine in terms of people who ever use the substance and go on to develop a dependence syndrome (~1/3 for nicotine and ~1/4 for intravenous heroin and crack cocaine) despite the fact that the subjective effects of nicotine are substantially less euphorogenic than either heroin or cocaine.²⁶

DA, NA, and Neuroplasticity: Addiction as a Disease of Pathological Learning and Memory

Some have argued that addiction fundamentally represents a type of memory disorder where the neurobiological mechanisms of learning and memory become corrupted by drugs of abuse, resulting in maladaptive associative learning to drug-related stimuli than come to be more powerfully motivating than those related to biologically relevant stimuli.⁵ Regarding natural rewards and adaptive behavioral responses, burst firing of DA neurons in the NA begins a process of reward-related neuroplasticity or learning that initially serves to alert that a novel salient stimuli has been encountered and to start to encode this event.²⁷ Some have likened DA's function in this mesolimbic pathway to playing a rheostatic role in learning the motivational significance of a stimulus (ie, better than expected vs worse than expected).⁹ Over time, however, as the motivational behavior becomes learned and familiar, DA release is no longer induced by this fully predicted reward but instead occurs in response to the most distal conditioned stimuli that come to predict the rewarding event.²⁸ In this way, DA alerts the individual through associative learning that a natural reward is coming or that an adaptive behavioral response can be predicted, and DA release gets transferred from the motivational to neutral stimuli. This is in contrast to drugs of abuse that are able to increase NA DA levels far greater than that of biologically rewarding stimuli and continue to release elevated DA levels upon each drug administration. This pharmacologically induced, enhanced, and sustained DA increase relative to biological stimuli causes more intense learned associations with neutral environmental stimuli, and the brain gets the message that these events are "better than expected," and that drug-related stimuli would theoretically be associated with a more intense stamping in of environmental stimuli that come to predict reward over biologically relevant ones.⁵ This "overlearning" of drug-acquisition behaviors is thought to play a significant role in the initiation of the addiction cycle and explaining enhanced vulnerability to craving and relapse by cue-induced environmental triggers.²⁹

Transition from Reward to Addiction:

The Hypothalamic-Pituitary-Adrenal Axis and the Stress System: Withdrawal and Negative Reinforcement

In the transition from abuse to dependence, all major drugs of abuse activate the brain stress systems, resulting in elevated adrenocorticotrophic hormone, corticosterone, and corticotrophin releasing factor (CRF) in the amygdala during acute withdrawal.³⁰ Moreover, CRF1 antagonists have been shown to decrease cocaine self-administration, withdrawal from several drugs of abuse, and stress-induced reinstatement to opioid-, alcohol-, and cocaine-seeking behaviors in rats,^{31,32} whereas glucocorticoid receptor antagonists have been demonstrated to decrease the reinforcing properties of stimulants.³³ Taken together, activation of the brain stress systems seems to contribute to the negative reinforcement associated with withdrawal states and relapse in

the abstinent state. As a result, antistress pharmacotherapies such as CRF1 antagonists may represent a new class of antiaddictive medications and might be applicable to a broad spectrum of substance use disorders.

Reinstatement (Conditioned Relapse) Paradigms: Dopaminergic and Glutamatergic Alterations

As addiction progresses from initial use to compulsive, unrestrained drug use (including the risk for relapse in an abstinent state), the neurocircuitry and neurochemistry shifts from a DA-based behavioral system (involved in the initial rewarding aspects of drug intake) to a predominantly glutamate-based one, yet one that continues to rely on the influence of DA release (Fig. 1).^{3,29} In the laboratory setting, after extinction of compulsive drug administration, 3 reinstatement paradigms (conditioned cues, drug priming, and stress) have been examined, all able to rapidly reinstate drug-seeking behavior or relapse to a previously established addicted state.³⁴ In the transition from drug use to a dependence syndrome, the main function of DA shifts from release in the NA (signaling initial reward and beginning the process of conditioned learning) with acute administration to release in the PFC and amygdala, and not the NA, to initiate the process of drug reinstatement or relapse, as well as release in the caudate (corticostratial circuitry) in modulating habit responding.²⁹ The afferent dopaminergic projections from the VTA to the PFC (mesocortical) and to the amygdala (mesolimbic) are necessary in the reinstatement process because drug-seeking behavior (initiated by all 3 reinstatement conditions) can be inhibited by inactivating the VTA.³⁵⁻³⁷ Specifically, conditioned-cue reinstatement involves DA release into the PFC and basolateral amygdala, drug-primed reinstatement likely involves DA release into the PFC and NA shell, and stress-induced reinstatement involves CRF and noradrenergic inputs into the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis with perhaps a modulatory role for DA in the mesocortical pathway.³⁸ Dopamine release in the PFC and amygdala in the reinstatement paradigms stimulates glutamatergic transmission between the PFC and amygdala and glutamate release in the pathway from the PFC to the NA core, constituting a "final common pathway" for initiating drug-seeking behavior.²⁹ Evidence for this comes from the following: enhanced glutamate release follows drug- and stress-induced reinstatement; all 3 reinstatement models can be prevented by lesioning the PFC in rats; and antiglutamatergic treatments can prevent drug seeking such as those that block the release of glutamate and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate antagonists, which can prevent cue-conditioned and drug-priming reinstatement when injected into the NA.³

In addition to this glutamatergic dysregulation in connections from the PFC to the NA, basal extracellular levels of glutamate in the NA are reduced in the addicted state such as with repeated cocaine administration and is associated with a reduced affinity of cystine for the cystine-glutamate nonsynaptic transporter.³⁹ In addition, in psychostimulant addiction, there is a downregulation in signaling in release-regulating presynaptic metabotropic glutamate receptors (mGluR2/3) that is likely associated with increased glutamate release in response to drug-paired cues.⁴⁰ Increases in extracellular glutamate from the cystine-glutamate exchanger stimulates the mGluR2/3 autoreceptors, which in turn can serve to attenuate presynaptic release of glutamate. Taken together, agents that increase extracellular glutamate in the NA by either using cysteine prodrugs that in turn activate the mGluR2/3 receptors or direct mGluR2/3

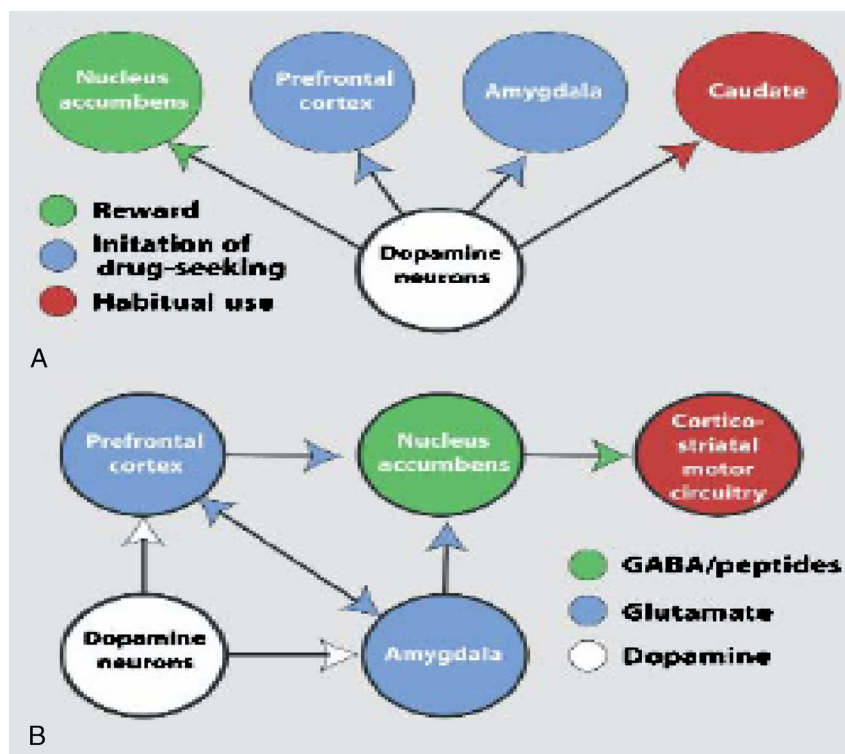


FIGURE 1. Addiction circuitry. A, Schematic and oversimplified sagittal view of a brain depicting 4 circuits that are postulated to have key interdependent and overlapping roles in addiction: 1) reward prediction and the core substrates of pleasure (red) located in the NAcc and VP; 2) memory and learning and the main substrate of conditioning (purple) located in the Amyg and HIP; 3) motivation, drive, and salience evaluation (green) located in the OFC; and 4) cognitive control (blue), in charge of restraining cravings, located in the PFC and ACG. B, Hypothetical model of addiction as the result of impaired information processing within the reward network. Compared with the nonaddicted state (left), the salience value of a drug (red) and its associated cues (purple) is enhanced in the addicted state (right), whereas the strength of inhibitory control is weakened (blue), setting up the stage for an unrestrained motivation (green), resulting in compulsive drug taking without regard to potentially catastrophic consequences. ACG indicates anterior cingulate gyrus; Amyg, amygdala; HIP, hippocampus; NAcc, nucleus accumbens; VP, ventral pallidum. Reprinted with permission (awaiting final permission) from *Trends Mol Med.* 2006;12(12):559–566.

agonists may have antiaddictive properties. The procysteine drug *N*-acetylcysteine restores extracellular levels of glutamate, which may in turn restore inhibitory tone by activating mGluR2/3 receptors, and has been shown to block reinstatement of cocaine use in animals⁴¹ and was associated with a reduction in cocaine craving in a trial of cocaine dependent patients.⁴² Moreover, specific mGluR2/3 agonists have been associated with diminished cocaine seeking in animals.⁴³

Executive Dysfunction Component of Addiction

Dysfunction of critical prefrontal cortical structures has emerged as a relatively new piece of the puzzle in trying to understand some core deficits seen in the addicted state such as loss of control, impulsivity, and impaired decision-making capacity related to weighing the relative saliency of competing reinforcers. Two important structures to consider are the orbitofrontal cortex (OFC) and the anterior cingulate gyrus (AC). The OFC is a paralimbic region, anatomically connected with prefrontal cortical areas mediating executive function, limbic structures, and association areas of sensory modalities, that integrates physical and affective components of an environmental stimuli and assigns a motivational value based on a prediction of reward, otherwise known as "salience attribution."⁴⁴ This important function helps an individual weigh the pros and cons of engaging in particular behaviors, and impairment of the OFC

would be predicted to result in drug craving and impaired decision making where drug-related stimuli would be erroneously deemed to have greater salience value than natural reinforcers. An important function of the AC is its role in inhibitory control of behaviors, and a reduction in activity of the AC has been associated with an inability of cocaine addicts to control urges to procure the drug.⁴⁵ Neuroimaging studies of craving in addicted subjects who are abstinent reveal that on a background of reduced basal activity of the OFC and AC, self-report of cue-induced craving is correlated with increased activity of the OFC and AC, whereas other studies have revealed decreased activity of these 2 regions in response to biologically oriented stimuli and decision-making tasks.³ In addition, after repeated and sustained drug use causing elevated DA levels in the NA, a marked reduction in dopamine function occurs. Imaging studies have revealed both a decrease in dopamine release in the NA and decreased striatal D2 receptors.⁴⁶ Taken together, a picture emerges of PFC executive dysfunction of impaired decision-making capacity and poor cognitive control whereby drug-related stimuli cause intense activation of the final common pathway (glutamatergic) of drug seeking from the PFC to the NA, whereas biologically relevant rewards produce hypoactive responses. All this on a background of reduced DA functioning in the NA, further impairing the individual's ability to signal the importance of natural or novel rewards worth paying attention to.

Summary/Overview

A useful model in trying to integrate the various previously mentioned independent and overlapping circuits that have come to be identified with addiction neurocircuitry has been proposed by Volkow and includes at a minimum the following 4 neural pathways (Fig. 2): 1) primary reinforcing effects of drugs of abuse and initiation of neuroplastic changes associated with memory formation in the mesolimbic dopaminergic pathway from the VTA projecting to limbic structures (NA, ventral pallidum); 2) memory consolidation associated with conditioned learning of drug-related stimuli in the amygdala and hippocampus, part of the mesolimbic pathway; 3) motivation, drive, regulation of emotional responses, and salience attribution of environmental stimuli in the OFC, part of the mesocortical pathway with afferent dopaminergic neurons projecting from the VTA; 4) cognitive and executive inhibitory control functions of the PFC and the AC, also part of the mesocortical pathway.^{6,47} In addition to the dopaminergic modulation of these pathways, they also interact with each other predominantly through GABAergic (inhibitory) and glutamatergic (excitatory) connections. In summary, it seems that the mesolimbic dopaminergic pathway mediates the acute rewarding aspects of drug intake and conditioned learning associated with craving and relapse, whereas adaptations in the mesocortical and corticofugal glutamatergic pathways mediate the conscious aspects of drug intake, craving, loss of inhibitory control, and continued drug-acquisition behaviors at the expense of biologically relevant ones and despite catastrophic negative consequences.³⁸ Besides these fundamental circuits, other brain regions and systems likely have modulatory functions such as brain stress systems dysregulated in the addictive process (ie, changes in adrenocorticotrophic hormone, corticosterone, and CRF), the insula

(modulation of internal emotional responses and autonomic activity involved in drug craving), the thalamus (filtering functions), the cerebellum, and the subthalamic nuclei.⁶

PHARMACOTHERAPY TO TREAT ADDICTIVE DISORDERS

Overall Goals

Broadly, the goals of pharmacotherapeutic treatment for addictive disorders includes 1) treating intoxication and withdrawal syndromes; 2) treatment to induce abstinence; 3) treatment to reduce substance use; 4) relapse prevention to both maintain abstinence and use reduction. The key in picking a pharmacotherapy to treat addictive disorders is to consider the stage of illness and the nature of disease progression. A theoretical prevention approach, not currently available, is to identify and treat high-risk individuals to prevent addiction initiation. Immune therapy (ie, vaccinations) might be a possible future example of such a treatment approach to prevent substance use from progressing to abuse and dependence syndromes. Other prevention strategies at other stages include preventing the progression from abuse to dependence and preventing relapse in abstinent individuals. It is key to consider the known neurobiological mechanisms underlying each stage so as to pick a medication suitable for the particular pathology of the particular stage.

Theoretical Overview of Treatment Approaches

Key to understanding the current and promising future pharmacotherapies for addictive disorders, it is important to lay out a theoretical framework of treatment that is rooted in the neuroscience of the addictive process. Two approaches might

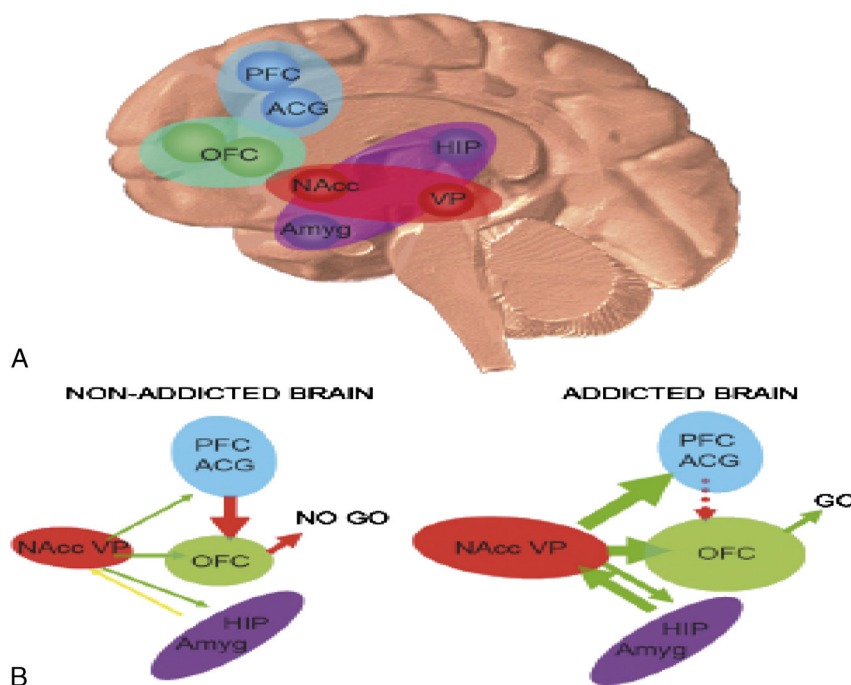


FIGURE 2. Models of the circuitry regulating the transition from psychostimulant reward to relapse. A, Dopamine projections and how chronic psychostimulant use produces a transition from reliance on accumbens DA for drug reinforcement to reliance on the prefrontal and amygdala DA to trigger relapse, to DA in the caudate in regulating habit responding. B, The circuitry in which DA projections are embedded that initiates relapse to drug-taking. Dopamine input to the amygdala and prefrontal cortex is critical, as is the glutamatergic output from these regions to the NA (awaiting final permission).

include disruption of the acute reinforcing and conditioning effects of drugs of abuse and compensatory neuroplastic brain changes related to chronic substance abuse.⁶

Disrupting the Acute Reinforcing and Conditioning Effects of Drugs (Positive Reinforcement and Learning)

One approach, interrupting the primary reinforcing and conditioning properties of a drug of abuse, could be useful at various stages of illness such as primary prevention (ie, the progression from use to abuse), progression from abuse to dependence, and relapse prevention. Within the category of interfering with drug reinforcement and conditioned learning, antiaddictive pharmacotherapies either act directly or through indirect processes to interrupt the acute increases in DA that promote addictive behaviors through either increases of DA in the NA mediating acute reward and initiating conditioned learning or increases in the amygdala, hippocampus, and PFC that are part of the relapse process as previously described.

First, a common approach is agonist substitution (blockade) or replacement therapy, where an addictive agent is replaced with one that has less addictive liability based on pharmacodynamic and pharmacokinetic characteristics such as receptor potency/affinity (ie, agonist, partial agonist, antagonist), rate of central nervous system absorption (ie, slower rates of absorption associated with less addictive liability) and half-life (ie, receptor, distribution, elimination with longer duration preferable). Such replacement therapies act as functional antagonists by binding to the receptor and preventing other similar but more addictive substances from binding to the receptor. Examples of this approach include methadone (long-acting pure μ opioid agonist) and buprenorphine (long-acting partial μ opioid agonist) for opiate use disorders and nicotine replacement and varenicline (long-acting partial cholinergic $\alpha_4\beta_2$ agonist) for nicotine use disorders (ie, tobacco smoking).^{48,49} For cocaine dependence, replacement with dopamine reuptake inhibitors (ie, vanorexine) with slow onset and long duration of action have been tried as substitution therapy,⁵⁰ and marinol is another replacement option to treat inhaled cannabis use disorders.

Another approach is to use agents that will diminish DA increases in the NA by affecting dopaminergic, GABAergic, opioidergic, serotonergic, cholinergic, or endocannabinoid systems involved in drug reinforcement. One way to achieve this would be to prevent the delivery of the addictive agent to the receptor site that mediates the drug's addictive liability as a way to completely or partially interfere with the reinforcing properties of a particular drug. One such approach is the use of receptor antagonists. For instance, naltrexone (μ -opioid antagonist) can directly and completely interrupt the rewarding effects of opiates (whose addictive liability is mediated solely via interactions with the μ opioid receptor), whereas it indirectly and only partially affects the addictive process in patients with alcohol use disorders, where the addictive liability is mediated by multiple receptors, including the μ opioid receptor.⁵¹ Cannabinoid type I receptor antagonists (ie, rimonabant) similarly hold the promise for directly interfering with the addictive process with cannabis dependence but also may be useful indirectly for other addictive disorders such as nicotine and obesity.⁹ Another new method being studied to prevent delivery of the addictive substance to its receptor site is the use of immune therapy to treat addictive disorders where vaccination and the production of antidrug antibodies have the potential to prevent the addictive drug from reaching the central nervous system and the receptor site of addictive liability.

There are preliminary data on the efficacy of vaccinations for nicotine, cocaine, and methamphetamine.⁵² Another approach would be to use DA receptor antagonists. Nonselective DA antagonists (ie, haloperidol, tiapride) have been associated with increased abstinence and decreased drug- and cue-induced craving in humans, although their neurotoxic side effects limit their clinical use.^{53,54} Specific D1 and D3 antagonists have shown promise in both animal and human studies as having potential antiaddictive.⁹ Examples of GABAergic agents that have antiaddictive properties include baclofen, tiagabine, vigabatrin, topiramate, and valproic acid for cocaine dependence and baclofen and topiramate for alcohol dependence, and an example of a serotonergic agent is ondansetron (5HT3 antagonist) for cocaine and alcohol dependence.^{50,51}

Third, agents that can trigger aversive responses can prevent addiction in the first place by behavioral conditioning and learned responses to the primary drug and conditioned cues, as well as preventing disease progression or relapse by behavioral counterconditioning. Lower prevalence of alcohol use disorders in Asians due to a relative or absolute deficiency of aldehyde dehydrogenase is an example of the former,⁵⁵ and the use of disulfiram (an aldehyde dehydrogenase inhibitor) to treat alcoholism is an example of the latter. Disulfiram may also cause an aversive reaction in cocaine-dependent patients related to its antagonist effects on DA- β -hydroxylase, leading to a build-up of postsynaptic DA that may be exacerbated by cocaine use, causing an aversive hyperdopaminergic state.⁵⁶

Compensation for Neuroplastic Brain Changes Related to Chronic Substance Abuse

Pharmacotherapies aimed at relapse prevention are rooted in the neurobiology of the drug reinstatement paradigms previously mentioned. Regarding conditioned cue relapse, a general goal would be to interrupt conditioned memories to the substance of abuse and its associated triggers.⁶ As mentioned, a core component underlying the transition from drug abuse to dependence relates to alterations in glutamatergic transmission whereby there is a hyperglutamatergic response from the PFC to NA as a final common pathway of drug-seeking behaviors triggered by drug-related stimuli and a relative hypoglutamatergic in response to "natural" rewards or cues. One could see a role for combined pharmacotherapy and cognitive-behavioral therapy. For instance, adding a glutamate blocking agent or one that serves to activate the mGlu2/3 autoreceptors (causing a reduction in presynaptic glutamate release) while exposed to drug-related cues could diminish drug-seeking behavior. Acamprosate is an example of an agent with glutamatergic stabilizing properties that, when used in combination with psychosocial treatment (ie, relapse prevention), is effective in increasing rates of total abstinence, cumulative abstinence duration, and time to first drink.⁵⁷ It is used to treat protracted withdrawal in alcohol dependence, presumably associated with continued perturbations and hyperexcitability of the PFC glutamatergic system.¹⁹ Similarly, adding a proglutamatergic agent while being exposed to biologically relevant stimuli could theoretically help increase the relative importance of such natural rewards or promote important new learning associated with sobriety. Somewhat similar to this are the efficacy data of the use of D-cycloserine (a partial NMDA agonist) and behavioral therapy (ie, exposure therapy) to reduce fear-conditioned behaviors.⁵⁸

In addition, given that DA release in the amygdala and PFC is antecedent and obligatory to the release of glutamate from the PFC to the NA-mediating conditioned relapse, it would

make theoretical sense to use DA blocking agents selective for these pathways while at the same time not blocking DA release in the NA when a novel salient natural reward is encountered. Another approach, based on the hypofunctioning of DA release in the NA in the addicted state impairing the ability to signal novel or biologically rewarding stimuli, would be to enhance DA function in the NA (mesolimbic pathway) to strengthen the saliency of natural rewards.⁶ Having agents that have such site specificity would be important, although likely difficult to develop as pharmacotherapies for addiction.

Interruption of the stress response system is a theoretical future target of treatment such as CRF 1 and glucocorticoid antagonists because, as mentioned, stress plays an important role in withdrawal states, negative reinforcement, and relapse.⁷

REFERENCES

- Kalivas PW, O'Brien C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* 2008;33:166–180.
- Volkow ND, et al. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 2006;26:6583–6588.
- Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 2005;162:1403–1413.
- Paulas MP. Neural basis of reward and craving—a homeostatic point of view. *Dialogues Clin Neurosci* 2007;9:379–387.
- Hyman SE. Addiction: a disease of learning and memory. *Am J Psychiatry* 2005;162:1414–1422.
- Baler RD, Volkow ND. Drug addiction: the neurobiology of disrupted self-control. *Trends Mol Med* 2006;12(12):559–566.
- Koob GF. Neurobiology of addiction. In: Galanter M, Kleber HD, eds. *Textbook of Substance Abuse Treatment*. 4th ed. Arlington, VA: American Psychiatric Publishing, Inc.; 2008:3–16.
- Kalivas PW. Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. *Brain Res Rev* 1993;18(1):75–113.
- Heidbreder C. Novel Pharmacotherapeutic targets for the management of drug addiction. *Eur J Pharmacol* 2005;526:101–112.
- Wise RA. Brain reward circuitry: insights from unsensed incentives. In: Graham AW, Schultz TK, Mayo-Smith MF, et al, eds. *Principles of Addiction Medicine*. 3rd ed. Chevy Chase, MD: American Society of Addiction Medicine Inc.; 2003:57–71.
- Grant JE, Brewer JA, Potenza MN. The neurobiology of substance and behavioral addictions. *CNS Spectr* 2006;11(12):924–930.
- Walsh SL, Cunningham KA. Serotonergic mechanisms involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. *Psychopharmacology (Berl)* 1997;130:41–58.
- Krystal JH, et al. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. *Psychopharmacology* 2003;169:215–233.
- Yonezawa Y, et al. Involvement of gamma-aminobutyric acid neurotransmission in phencyclidine-induced dopamine release in the medial prefrontal cortex. *Eur J Pharmacol* 1998;341:45–56.
- Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science* 1998;281:1349–1352.
- Bisaga A, Evans SM. Acute effects of memantine in combination with alcohol in moderate drinkers. *Psychopharmacology (Berl)* 2004;172:16–24.
- Krupitsky EM, Neznanova O, Masalov D. Effect of memantine on cue-induced alcohol craving in recovering alcohol-dependent patients. *Am J Psychiatry* 2007;164:519–523.
- Comer SD, Sullivan MA. Memantine produces modest reductions in heroin-induced subjective responses in human research volunteers. *Psychopharmacology* 2007;193(2):235–245.
- Littleton JM. Acamprosate in alcohol dependence: implications of a unique mechanism of action. *J Addic Med* 2007;1(3):115–125.
- Alper KR, Lotsof HS, et al. Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* 1999;8:234–242.
- Krupitsky E, Grineko A. Psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs* 1997;29(2):165–183.
- Krupitsky E, et al. Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *J Subst Abuse Treat* 2002;23:273–283.
- Ross S. Ketamine and addiction. *Primary Psychiatry* 2008;15(9):61–69.
- Roberts DC, et al. Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacol Biochem Behav* 1980;12:781–787.
- Wise RA. Action of drugs of abuse on brain reward systems. *Pharmacol Biochem Behav* 1980;13:213–223.
- Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol* 1994;2:244–268.
- Horvitz JC. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. *Neuroscience* 2000;96:651–656.
- Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* 1997;275:1593–1599.
- Kalivas PW. Cocaine and amphetamine-like psychostimulants: neurocircuitry and glutamate neuroplasticity. *Dialogues Clin Neurosci* 2007;9:389–397.
- Weiss F, et al. Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Ann N Y Acad Sci* 2001;937:1–26.
- Nie Z, et al. Ethanol augments GABAergic transmission in the central amygdala via CRF1 receptors. *Science* 2004;303:1512–1514.
- Shaham Y, et al. CP-15,526, a selective, non-peptide antagonist of the corticotrophin-releasing factor1 receptor attenuates stress-induced relapse to drug seeking cocaine- and heroin-trained rats. *Psychopharmacology (Berl)* 1998;137:184–190.
- Deroche-Gamonet, et al. The glucocorticoid receptor as a potential target to reduce cocaine abuse. *J Neurosci* 2003;23:4785–4790.
- Shaham Y, et al. The reinstatement model of drug relapse: history, methodology, and major findings. *Psychopharmacology (Berl)* 2003;168:3–20.
- McFarland K, et al. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* 2004;24:1551–1560.
- McFarland K, Kalivas PW. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2001;21:8655–8663.
- Di Ciano P, Everitt BJ. Contribution of the ventral tegmental area to cocaine-seeking maintained by a drug-paired conditioned stimulus in rats. *Eur J Neurosci* 2004;19:1661–1667.
- Feltenstein MW, See RE. The neurocircuitry of addiction: an overview. *Br J Pharmacol* 2008;154(2):261–274.
- Kalivas PW, et al. Glutamate transmission and addiction to cocaine. *Ann N Y Acad Sci* 2003;1003:169–175.
- Xi ZX, et al. Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. *J Pharmacol Exp Ther* 2002;303:608–615.

41. Baker DA, et al. Neuroadaptation in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003;6:743–749.
42. LaRowe S, et al. Cocaine desire is reduced by *N*-acetylcysteine. *Am J Psychiatry* 2007;164:1115–1117.
43. Peters J, Kalivas PW. The group II metabotropic glutamate receptor agonist, LY379268, inhibits both cocaine- and food-seeking behavior in rats. *Psychopharmacology (Berl)* 2006;186:143–149.
44. London ED, et al. Orbitofrontal cortex and human drug abuse: functional imaging. *Cerebral Cortex* 2000;10:334–342.
45. Hester R, Garavan H. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. *J Neurosci* 2004;24:11017–11022.
46. Volkow ND, et al. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry* 2004;9:557–569.
47. Volkow ND, et al. The addicted human brain: insights from imaging studies. *J Clin Invest* 2003;111:1444–1451.
48. Kleber HD. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. *Dialogues Clin Neurosci* 2007;9:455–470.
49. Gonzales D, et al. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296:47–55.
50. Preti A. New developments in the pharmacotherapy of cocaine abuse. *Addict Biol* 2007;12:133–151.
51. Tambour S, Quertemont E. Preclinical and clinical pharmacology of alcohol dependence. *Fundam Clin Pharmacol* 2007;21:9–28.
52. Kosten T, Owens MS. Immunotherapy for the treatment of drug abuse. *Pharmacol Ther* 2005;108:76–85.
53. Modell JG, Mountz JM, Glaser FB, et al. Effect of haloperidol on measures of craving and impaired control in alcoholic subjects. *Alcohol Clin Exp Res* 1993;17(2):234–240.
54. Shaw GK, Waller S, Majumdar SK, et al. Tiapride in the prevention of relapse in recently detoxified alcoholics. *Br J Psychiatry* 1994;165(4):515–523.
55. Thomasson HR, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. *Am J Hum Genet* 1991;48:677–681.
56. McCance-Katz EF, Kosten TR, Jatlow P. Chronic disulfiram treatment effects on intranasal cocaine administration: initial results. *Biol Psychiatry* 1998;43:540–543.
57. Mason BJ. Acamprosate and naltrexone treatment for alcohol dependence: an evidence-based risk-benefits assessment. *Eur Neuropsychopharmacol* 2003;13:469–475.
58. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry* 2008;63(12):1118–1126.